UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,298	12/18/2006	M. Ian Phillips	USF.200TCXZ1	6761

23557 7590 01/06/2011
SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/06/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/567,298	PHILLIPS ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11-13,16-19,28-31 and 33-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11-13,16-19,28-31 and 33-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim amendments filed on 10/04/2010 have been entered

Claims 7-10, 14, 15, 20-27, and 32 are cancelled. Claims 35 and 36 are newly added. Claims 1, 13, 28, and 34 are amended. Claims 1-6, 11-13, 16-19, 28-31, and 33-36 are pending.

Claims 1-6, 11-13, 16-19, 28-31, and 33-36 are currently under examination to the extent of elected species, as documented on pages 2-4 of the office action mailed on 07/22/2009, which are (i) mesenchymal stem cell (MSC), which has the capacity to differentiate into a cardiac cell, with respect to a genetically modified stem or progenitor cell, and (ii) heme oxygenase-1 (HO-1) gene with respect to a nucleic acid sequence encoding a therapeutic product, and (iii) hypoxia with respect to a physiological stimulus.

It is noted that upon further consideration and search, the requirement of species election between mesenchymal stem cell (MSC) and hematopoietic stem cells (HSCs) is withdrawn.

This application 10/567,298 is a 371 of PCT/US04/26195 filed on 08/11/2004 which claims benefit of 60/494,184 filed on 08/11/2003, and claims benefit of 60/494,185 filed on 08/11/2003, and claims benefit of 60/513,067 filed on 10/21/2003, and claims benefit of 60/513,657 filed on 10/23/2003.

Claim Objection

1. Claims 1 and 28 are objected to because of the following informalities: To improve the clarity of claim 1 and 28, it is advised that the limitation "wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter" should be stated as "wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator controlled by an operatively linked promoter" or

similar claim language supported by instant specification and/or the status of art. It is noted that the wherein clause as written, it appears that "an operatively linked promoter" is encoded by "said gene switch/biosensor". In this regard, a promoter is a polynucleotide sequence that controls/drives the expression of downstream coding sequence which encodes a polypeptide sequence. Appropriate correction is required.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Previous rejection of claims 1-6, 11-13, 16-19, 28-31, 33, and 34 under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, Hypertension, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Turgeman et al.** (Turgeman et al., Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy. J Gene Med. 3(3):240-51, 2001) and **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, Circulation, 104(13):1519-25, 2001), is **withdrawn** because the claims have been amended. Previous rejection of claims 7-9 and 32 is **moot** because these claims have been cancelled.

Amended claim 1 filed on 10/04/2010 reads as follows: A genetically modified stem or progenitor cell comprising: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive

chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product: wherein said therapeutic product is heme oxygenase-1 (HO-1); and wherein said first and second exogenous polynucleotides are provided in an adeno-associated virus (AAV) vector.

Amended claim 28 filed on 10/04/2010 reads as follows: A modified mammalian tissue, wherein said tissue comprises a genetically modified mammalian stem or progenitor cell, wherein said cell comprises: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product: wherein said therapeutic product is heme oxygenase-1 (HO-1); and wherein said first and second exogenous polynucleotides are provided in an adeno-associated virus (AAV) vector.

None of Tang et al. (2002), Turgeman et al. (2001) and Juan et al. (2001) explicitly teaches the amended limitation "wherein said first and second exogenous polynucleotides are provided in an adeno-associated virus (AAV) vector".

3. Previous rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, Hypertension, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Turgeman et al.** (Turgeman et al., Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy. J Gene Med. 3(3):240-51, 2001) and **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, Circulation, 104(13):1519-25,2001), as applied to claims 1-9, 11-13, 16-19, and 28-34 above, and further in view of **Nicklin et al.** (Nicklin et al., Tropism-modified adenoviral and adeno-

associated viral vectors for gene therapy, Curr Gene Ther. 2(3):273-93, 2002) is **moot** because claim 10 has been cancelled.

The following 103 rejection is necessitated by claim amendments filed on 10/04/2010 by Applicant.

4. Claims 1-6, 11-13, 16-19, 28-31, and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, Hypertension, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Turgeman et al.** (Turgeman et al., Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy. J Gene Med. 3(3):240-51, 2001), **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, Circulation, 104(13):1519-25, 2001), and **Nathwani et al.** (Nathwani et al., Efficient gene transfer into human cord blood CD34+ cells and the CD34+CD38- subset using highly purified recombinant adeno-associated viral vector preparations that are free of helper virus and wild-type AAV, Gene Ther. 7(3):183-95, 2000).

Amended claim 1 filed on 10/04/2010 reads as follows: A genetically modified stem or progenitor cell comprising: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product: wherein said therapeutic

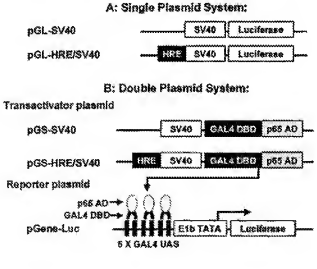
product is heme oxygenase-1 (HO-1); and wherein said first and second exogenous polynucleotides are provided in an adeno-associated virus (AAV) vector.

Amended claim 28 filed on 10/04/2010 reads as follows: A modified mammalian tissue, wherein said tissue comprises a genetically modified mammalian stem or progenitor cell, wherein said cell comprises: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product: wherein said therapeutic product is heme oxygenase-1 (HO-1); and wherein said first and second exogenous polynucleotides are provided in an adeno-associated virus (AAV) vector.

Claim interpretation: **(I)** The limitation "wherein said first and second exogenous polynucleotides are provided in an adeno-associated virus (AAV) vector" recited in claim 1 and 28 reads on (i) providing said first and second exogenous polynucleotides in different AAV vector molecule, and (ii) providing said first and second exogenous polynucleotides in the same AAV vector molecule by, for instance, a bicistronic rAAV vector. **(II)** The limitation "wherein said therapeutic product is a polypeptide that is endogenous to said cell" recited in claim 17 is interpreted as any therapeutic product that is a polypeptide encoded by a transgene (i.e. exogenous polynucleotide) and the genome of said cell comprises gene(s) on chromosomes that can encode the same polypeptide (which is considered endogenous to the said cell). **(III)** The limitation "A modified mammalian tissue" recited in claim 28 reads on (i) a mammalian tissue differentiated from the recited genetically modified mammalian stem cell, and (ii) a mammalian tissue comprises the recited genetically modified mammalian stem cell, which is transplanted to an existing mammalian tissue.

With regard to the limitations of claims 1-6, 8, 11, 12, 16-19, 28-31, and 33-36 of instant application, Tang et al. teaches that coronary artery disease frequently involves repeated bouts of

myocardial ischemia (which reads on hypoxia recited in claims 18, 19, and 33), and to automatically up-regulate the cardioprotective transgenes under hypoxic ischemia, a ""vigilant vector" gene therapy system was developed and tested in a rat embryonic cardiac myoblast (H9c2). Tang et al. teaches that, in the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal. Furthermore, Tang et al. teaches that a novel double plasmid system was designed to elevate the potency of the vigilant vector, and instead of putting the promoter and the reporter gene in the same plasmid (single plasmid system), Tang et al. separated them into two plasmids: the transactivator plasmid and reporter plasmid (double plasmid system). Tang teaches that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-kappaB (NF-kappaB) p65 activation domain (which reads on the limitations of claim 6 of instant application), and the chimeric regulator binds specifically to the upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene (See abstract and Figure 1 shown below, Tang et al., 2002).



Tang et al. does not explicitly teach **(I)** a genetically modified stem cell recited in claim 1 and a mesenchymal stem cell (MSC) or a hematopoietic stem cell (HSC) recited in claims 13 and 34; **(II)** a modified mammalian tissue recited in claim 28 and its dependent claims 29-31, 33, and 34; **(III)** a nucleic acid sequence encoding a therapeutic product recited in claim 1 and said therapeutic product being heme oxygenase-1 (OH-1) recited in claim 7 and adeno-associated virus (AAV) recited in claims 1 and 28 of instant application, and CMV promoter recited in claims 35 and 36.

However, at the time of filing of instant application, the limitations **(I)** a genetically modified stem cell recited in claim 1 and a mesenchymal stem cell (MSC) or a hematopoietic stem cell (HSC) recited in claims 13 and 34; **(II)** a modified mammalian tissue recited in claim 28 and its dependent claims 29-31, 33, and 34; **(III)** a nucleic acid sequence encoding a therapeutic product recited in claim 1 and said therapeutic product being heme oxygenase-1 (OH-1) recited in claim 7 and adeno-associated virus (AAV) recited in claims 1 and 28 of instant application, and CMV promoter recited in claims 35 and 36, are well known in the art in the context of gene transfer and expression in stem cells of interest.

(I) With regard to the limitation "a genetically modified stem cell" recited in claim 1 and "a mesenchymal stem cell (MSC)" recited in claims 13 and 34, **Turgeman et al.** teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types. Turgeman et al. teaches that hMSCs represent a novel platform for skeletal gene therapy and that hMSCs can be genetically engineered to express desired therapeutic proteins inducing specific differentiation pathways (See abstract, page 240, Turgeman et al.). Turgeman et al. further teaches in vitro characterization of adenoviral vector

comprising CMV promoter infected hMSCs and transplantation in ectopic sites of adenoviral vector infected hMSCs (See pages 142-242, Turgeman et al., 2001).

(II) With regard to the limitation "a modified mammalian tissue" recited in claim 28, the limitation "a human cell" recited in claim 29, the limitation "said cell is autologous to said tissue" recited in claim 30, and the limitation "mesenchymal tissue" recited in claim 31, **Turgeman et al.** teaches that genetically engineered hMSCs displayed enhanced proliferation and osteogenic differentiation in culture; in vivo, transplanted genetically engineered hMSCs were able to engraft and form bone and cartilage in ectopic sites, and regenerate bone defects (non-union fractures) in mice radius bone; and importantly, the same results were obtained with hMSCs isolated from a patient suffering from osteoporosis (See abstract and Figure 4, Turgeman et al., 2001). It is noted that the formation of new bone and cartilage in ectopic sites comprising cells differentiated from hMSCs taught by Turgeman et al. (2001) reads on the limitation "mesenchymal tissue" recited in claim 31, and the limitation "said cell is autologous/syngenic to said tissue" recited in claim 30.

(III) With regard to a nucleic acid sequence encoding a therapeutic product recited in claim 1 and said therapeutic product being heme oxygenase-1 (OH-1) recited in claim 7, **Juan et al.** teaches the followings: (i) adenovirus-mediated gene transfer of HO-1 (which reads on claims 9 and 32 of instant application) in arteries reduces iron overload and inhibits lesion formation in apolipoprotein E (apoE)-deficient mice (See abstract, Juan et al., 2001), and (ii) heme oxygenase (HO) is a rate-limiting enzyme in heme catabolism; one of the isozymes, HO-1, is a stress-response protein and can be induced by a variety of oxidation-inducing agents, including heme/hemoglobin, heavy metals, UV radiation, cytokines, and others, and induction

of HO-1 leads to the degradation of pro-oxidant heme to carbon monoxide (CO) and biliverdin (See introduction, page 1519, Juan et al., 2001).

With regard to the limitation "adeno-associated virus (AAV)" in the context of stem cell transfection recited in claim 1, **Nathwani et al.** discloses various viral vectors used for transducing human cells and the properties of recombinant AAV (rAAV) vectors that make them attractive for hematopoietic stem cell (HSC) transduction (See Introduction, page 183, Nathwani et al., 2000). Nathwani et al. teaches using improved methodology to generate high titer, biologically active preparations of rAAV free of wild-type AAV (less than $1/10^7$particles) and adenovirus. Nathwani et al. further teaches transduction of CD34+ cells from umbilical cord blood was evaluated with a bicistronic rAAV vector encoding the green fluorescent protein (GFP) and a trimetrexate resistant variant of dihydrofolate reductase (DHFR). Nathwani et al. teaches that under optimal conditions 41 +/- 7% of CD34+ progenitors and 21 +/- 6% of CD34+, CD38- progenitors became trimetrexate resistant (See abstract, Nathwani et al., 2000). Nathwani et al teaches schematic diagram of AAV vector and split packaging plasmid construction with CMV promoter (See Figure 1(d) and 1(e), shown below, Nathwani et al., 2000).

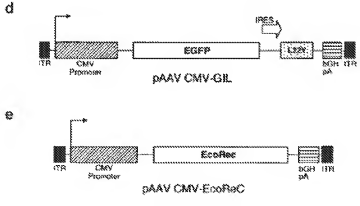


Figure 1 Schematic diagram of AAV vector and split packaging plasmid construction. (d) Illustration of the AAV vector pAAV CMV-GIL. The pSUB201-derived AAV inverted

terminal repeats (ITR) flank a bicistronic expression cassette under the control of the CMV IE promoter. This construct contains the internal ribosomal entry site (IRES) from the encephalomyocarditis virus that allow the expression of the enhanced green fluorescent protein (EGFP) and the L22Y variant of the dihydrofolate reducates gene (L22Y). (e) Schematic representation of pAAV CMV-EcoRec in which the CMV IE promoter directs the expression of the murine ecotropic retrovirus receptor (EcoRec).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of **(i)** Tang et al. regarding a genetically modified/transfected cell comprises two plasmids: the transactivator plasmid and reporter plasmid and that that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-kappaB (NF-kappaB) p65 activation domain, and the chimeric regulator binds specifically to the upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene, with the teachings of **(ii)** Turgeman et al. regarding the use genetically engineered hMSCs for gene therapy to express desired therapeutic proteins, whereas the hMSCs can be directed to specific differentiation pathways to form mesenchymal tissue, and the teachings of **(iii)** Juan et al. regarding expressing HO-1 gene from an adenoviral vector for therapeutic purpose, and Nathwani et al. regarding transduction of CD34+ cells from human umbilical cord blood with a bicistronic rAAV vector encoding the green fluorescent protein (GFP) and a trimetrexate resistant variant of dihydrofolate reductase (DHFR), to arrive at the claimed genetically modified stem cell comprising expression cassette as recited in claims 1-6, 11-13, 16-19, 28-31, and 33-36 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Tang et al., Turgeman et al., Juan et al., and Nathwani et al. because (i) Tang et al. establishes the double plasmid system sensitive to hypoxia condition for gene therapy of coronary artery disease by monitoring the expression of luciferase as a reporter, (ii) Turgeman et al. teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types and hMSCs can function as a transgene vehicle and can be genetically engineered to express desired therapeutic proteins and the genetically engineered hMSCs can be induced toward specific differentiation pathways to form mesenchymal tissue for treatment, and (iii) Juan et al. teaches Adv-OH-1 construct (which expresses OH-1 from an adenoviral vector) for gene therapy of atherosclerosis since HO-1 is a stress-response protein and can be induced by a variety of oxidation-inducing agents, and (iv) Nathwani et al. teaches improved methodology for efficient gene transfer into CD34+ stem cells. Moreover, transfection of DNA into different cells of interest is prima facie obvious to a skilled artisan as clearly demonstrated by Tang et al., Turgeman et al., and Nathwani et al. In this regard, it is prima facie obvious for a skilled artisan to transfect the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal, taught by Tang et al., to the hMSC taught by Turgeman et al., instead of "embryonic cardiac myoblast" taught by Tang et al. because Turgeman et al. specifically teaches that genetically engineered hMSCs displayed enhanced proliferation and osteogenic differentiation in culture; in vivo, transplanted genetically engineered hMSCs were able to engraft and form bone and cartilage in ectopic sites, and regenerate bone defects (non-union fractures) in mice radius bone; and importantly, the same results were obtained with hMSCs isolated from a patient suffering from osteoporosis (See

abstract and Figure 4, Turgeman et al., 2001). Additionally, substitution of a reporter gene taught by Tang et al. with a gene encoding a therapeutic protein (HO-1 gene taught by Juan et al.) in the context of a vector, either a plasmid or a viral vector, is a common practice in molecular biology depending on the gene of interest to be expressed. Furthermore, substitution of SV40 promoter, taught by Tang et al. 2002, with the CMV promoter taught by Nathwani, is prima facie obvious to a skilled artisan because both promoters are well established and commonly used strong promoters in molecular cloning to express a gene of interest.

There would have been a reasonable expectation of success given (i) the successful construction of double plasmid system and transfection/expression of the double plasmid system in rat embryonic cardiac myoblast cell line by the teachings of Tang et al., (ii) demonstration of genetically engineered human mesenchymal stem cells expressing human BMP-2 from an adenoviral vector leading to formation of cartilage and bone in vivo for treatment of osteoporesis by the teachings of Turgeman et al., (iii) the transfection and expression of Adv-OH-1 construct for gene therapy of atherosclerosis by the teachings of Juan et al., and (iv) the demonstration of efficient gene transfer into human CD34+ stem cells using highly purified recombinant adeno-associated virus (AAV) by the teachings of Nathwani et al.

Thus, the claimed invention as a whole was clearly prima facie obvious.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and KSR Guidelines Update

has been published in the Federal Register at 75 Fed. Reg. 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine Tang et al., Turgeman et al., Juan et al., and Nathwani et al. has been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments

Applicant argues that as Applicants have discussed in response to previous Office Actions, the claimed invention provides cells, such as adult stem cells derived from bone marrow, a novel and surprising means of surviving in a hostile environment (such as in an injured heart where oxygen levels are very low). When unmodified bone marrow stem cells are transplanted into ischemic hearts, the majority of the engrafted cells (over 90%) die within 1-2 days. Thus, it was not obvious to provide cells with means for surviving in the hostile environment because the high rate of death of implanted stem cells was not known in the art at the time of the present invention. Applicants assert that this point is not addressed in the current Office Action, nor is it taught or suggested in any of the cited references. In regard to this issue, the Examiner simply states in the current Office Action that "It should be emphasized that 'surviving in a hostile environment (such as in an injured heart where oxygen levels are very low)' is taught by the primary reference Tang et al., not Turgeman et al." The Examiner has not rebutted Applicants' assertion or pointed out where in any of the cited references, including Tang et al., it is taught that stem cells transplanted into ischemic tissue have a high death rate (over 90%). Applicants note that a combination of elements is not prima facie obvious if an ordinarily skilled artisan would not have recognized an apparent reason to combine the elements. KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 1741 (2007); Ecolab, Inc. v. FMC Corp., 569

F.3d 1335 (Fed. Cir. 2009). Applicants respectfully assert that there was no apparent reason to combine the elements because, as noted above, the high rate of death of implanted stem cells in a hostile tissue environment was not known in the art at the time of the invention (See page 7 of Applicant's remarks filed on 10/04/2010).

Applicant argues that the Fukuda reference only discloses that a cardiomyogenic cell line could be isolated from bone marrow mesenchymal stem cells and discusses that such cells could possibly be used in cell transplantation therapy for heart failure. The Fukuda reference does not disclose that stem cells implanted in ischemic tissue have a very high death rate. Thus, an ordinarily skilled artisan at the time of the invention expected that implanted stem cells had a typical cell survival rate and, therefore, the artisan would **not** have been concerned with or motivated for finding ways to improve stem cell survival rate. It is only the subject application that teaches the problem and provides a solution to the problem in the form of the claimed invention (See page 8 of Applicant's remarks filed on 10/04/2010).

Applicant argues that the Tang et al. reference describes testing different types of gene switches, including single vector and double vector models. The rat myoblast cell line H9c2 referred to in the Tang et al. reference was only used for testing the vector. It was not used for stem cell transplantation. The authors of the Tang et al. reference did not teach or suggest an approach for improving stem cell survival when the cells are transplanted into injured tissue, such as ischemic heart tissue. The work reported in the Tang et al. reference is directed solely to development of an injectable gene switch which would reside in specific body tissue, such as heart ventricle, defined by the promoter incorporated into the gene switch. Thus, a person of ordinary skill in the art would not have looked to the Tang et al. reference for teachings relevant to the preparation of Applicants' claimed invention (See page 8 of Applicant's remarks filed on 10/04/2010).

Applicant states that Applicants maintain that the cited references do not teach or suggest a mammalian tissue comprising a genetically modified mammalian stem or progenitor cell as claimed in claims 28-34. There is no teaching or suggestion in any of the cited references to provide mammalian tissue with a genetically modified stem cell or progenitor cell of the invention. As noted above, the Tang et al. reference is concerned with direct gene therapy in a tissue and is not conceived with cell therapy. Thus, Tang et al. is only relevant with regard to

transforming cells already present within a tissue with a nucleic acid vector. As noted previously, the intended use of the genetically modified stem cell or progenitor cell is discussed to point out why a person of ordinary skill in the art would not look to the teachings of the cited references, i.e., because they are directed to uses that are not relevant to the claimed invention. It was only the inventors of the claimed invention that realized the problem to be solved and did so by invention of the claimed genetically modified cell and mammalian tissue comprising the genetically modified cell.

Response to Applicant's *arguments*

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above. It is noted that **(i)** previous rejection of claims 1-6, 11-13, 16-19, 28-31, 33, and 34 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (2002) in view of Turgeman et al. (2001) and Juan et al. (2001), has been withdrawn, and **(ii)** previous rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (2002) in view of Turgeman et al. (2001) and Juan et al. (2001), as applied to claims 1-9, 11-13, 16-19, and 28-34 above, and further in view of Nicklin et al. (2002) is moot.

Applicant is reminded that the claimed invention is a product directed to a genetically modified stem or progenitor cell, not a method for "improving stem cell survival when the cells are transplanted into injured tissue, such as ischemic heart tissue" as Applicant argued. In this regard, as responded previously, the Examiner maintains the position that intended use of claimed products bears limited, if any patentable weight. Intended used does not impart patentable weight to a product. See MPEP 2111.03:

> Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459, (CCPA 1963).

The argument of "improving stem cell survival when the cells are transplanted into injured tissue, such as ischemic heart tissue" is the intended use of claimed "genetically modified stem cells". Furthermore, it is worth noting that nowhere in the claims recites the requirement of "improving stem cell survival when the cells are transplanted into injured tissue" of claimed genetically modified stem or progenitor cells.

"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), Northam Warren Corp. v. D. F. Newfield Co., 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934.) See MPEP 2113 and MPEP 2112.01.

With regard to the "apparent reason" why the claimed "genetically modified stem cells are prima facie, Turgeman et al. specifically teaches that human mesenchymal stem cells (hMSCs) represent a novel platform for skeletal gene therapy and that hMSCs can be genetically engineered to express desired therapeutic proteins inducing specific differentiation pathways (See abstract, page 240, Turgeman et al.). Transfection of DNA into different cells of interest is prima facie obvious to a skilled artisan as clearly demonstrated by Tang et al., Turgeman et al., and Nathwani et al. In this regard, it is prima facie obvious for a skilled artisan to transfect the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal, taught by Tang et al., to the hMSC taught by Turgeman et al., instead of "embryonic cardiac myoblast" taught by Tang et al.

For the clarity of record, the new grounds of rejection documented in this office action states the followings: One having ordinary skill in the art would have been motivated to combine the teachings of Tang et al., Turgeman et al., Juan et al., and Nathwani et al. because (i) Tang et al. establishes the double plasmid system sensitive to hypoxia condition for gene therapy of

coronary artery disease by monitoring the expression of luciferase as a reporter, (ii) Turgeman et al. teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types and hMSCs can function as a transgene vehicle and can be genetically engineered to express desired therapeutic proteins and the genetically engineered hMSCs can be induced toward specific differentiation pathways to form mesenchymal tissue for treatment, and (iii) Juan et al. teaches Adv-OH-1 construct (which expresses OH-1 from an adenoviral vector) for gene therapy of atherosclerosis since HO-1 is a stress-response protein and can be induced by a variety of oxidation-inducing agents, and (iv) Nathwani et al. teaches improved methodology for efficient gene transfer into CD34+ stem cells. Moreover, transfection of DNA into different cells of interest is prima facie obvious to a skilled artisan as clearly demonstrated by Tang et al., Turgeman et al., and Nathwani et al. In this regard, it is prima facie obvious for a skilled artisan to transfect the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal, taught by Tang et al., to the hMSC taught by Turgeman et al., instead of "embryonic cardiac myoblast" taught by Tang et al. because Turgeman et al. specifically teaches that genetically engineered hMSCs displayed enhanced proliferation and osteogenic differentiation in culture; in vivo, transplanted genetically engineered hMSCs were able to engraft and form bone and cartilage in ectopic sites, and regenerate bone defects (non-union fractures) in mice radius bone; and importantly, the same results were obtained with hMSCs isolated from a patient suffering from osteoporosis (See abstract and Figure 4, Turgeman et al., 2001). Additionally, substitution of a reporter gene taught by Tang et al. with a gene encoding a therapeutic protein (HO-1 gene taught by Juan et al.) in the context of a vector, either a plasmid or a viral vector, is a common practice in molecular biology depending on the gene of interest to be expressed. Furthermore, substitution of SV40 promoter, taught by Tang et al. 2002, with the CMV promoter taught by Nathwani, is prima facie obvious to a skilled artisan because both promoters are well established and commonly used strong promoters in molecular cloning to express a gene of interest.

With regard to the asserted requirement for specific TSM (teaching, suggestion, and motivation), as stated in the new grounds of 103(a) rejection, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v.

Teleflex, Inc. that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and KSR Guidelines Update has been published in the Federal Register at 75 Fed. Reg. 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine Tang et al., Turgeman et al., Juan et al., and Nathwani et al. has been clearly set forth above in this office action.

Applicant is reminded that the new ground of rejection is a 103(a) rejection, not a 102 rejection. In this regard, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Pages 12-13 of the non-Final office action mailed on 04/29/2010 documented the following statements: "Furthermore, relevant to Applicant's arguments pertaining to feasibility of stem cell therapy, it is worth noting that isolation of a cardiomyogenic cell line (CMG cell) from murine bone marrow mesenchymal stem cells and cell transplantation therapy for the patients with heart failure might be achieved using the regenerated cardiomyocytes from autologous bone marrow cells was known in the art before the claimed priority date of instant application (See for instance, Fukuda et al., Regeneration of cardiomyocytes from bone marrow: Use of mesenchymal stem cell for cardiovascular tissue engineering, Cytotechnology 41(2-3):165-175, 2003)". The Examiner agrees with Applicant's statements (page 8) filed on 10/04/2010, that "the Fukuda reference does not disclose that stem cells implanted in ischemic tissue have a very high death rate". Nevertheless, this reference was cited in the previous office action in the context of responding to "Applicant's arguments pertaining to feasibility of stem cell therapy", and this reference has in fact never been cited in any 103 rejection of the record. In this regard, as responded above in this office action, the argument of "improving stem cell survival when the cells are transplanted into injured tissue, such as ischemic heart tissue" is the intended use of

claimed "genetically modified stem cells". Furthermore, it is worth noting that nowhere in the claims recites the requirement of "improving stem cell survival when the cells are transplanted into injured tissue" of claimed "genetically modified stem or progenitor cells". The characteristics of claimed "genetically modified stem or progenitor cells" are inherent to the "genetically modified stem or progenitor cells" taught by the combined teachings of Tang et al., Turgeman et al., Juan et al., and Nathwani et al. In this regard, Applicant's attention is directed to MPEP 2112 [R-3], Requirements of Rejection Based on Inherency; Burden of Proof: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983). I. SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DIS-COVERY OF A NEW PROPERTY: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In In re Crish, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." Id.< See also MPEP § 2112.01 with regard to inherency and product-by-process claims and MPEP § 2141.02 with regard to inherency and rejections under 35 U.S.C. 103.

Conclusion

5. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632